matter has been added as a result of the above-described amendments. The rejections set forth in the Office Action have been overcome by amendment or are traversed by argument below.

1. Objection to claim 25

The Office Action contains an objection to claim 25 for failing to list the amino acids in the truncated KGF-2 protein of the invention using three-letter abbreviations and for failing to make reference to the claimed sequence using "SEQ ID NO:" and a sequence identifier. The complete sequence of the KGF-2 protein is set forth in SEQ ID NO: 2, and the sequence corresponding to the truncated KGF-2 protein of claim 25 is set forth as the portion of SEQ ID NO: 2 comprising amino acid residues 66 through 208. Applicants respectfully contend that claim 25, as amended, fully complies with 37 C.F.R. §§ 1.821(b) and (d) and 1.822(d). If the Examiner believes it to be necessary, Applicants will file an amended Sequence Listing, setting forth the truncated KGF-2 protein sequence as a separately-listed sequence, despite the claim's compliance with the applicable regulations.

2. Rejections of claims 6-8, 10-22, and 25-27 under 35 U.S.C. § 112, first paragraph

The Office Action asserts a rejection of claims 6-8, 10-22, and 25-27 under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for compositions of variants that are truncated forms of KGF-2, does not reasonably provide enablement for "any other variants" that could be used as pharmaceutical compositions for treatment of diseases. The Examiner takes the position that the phrase "[a] variant of keratinocyte growth factor-2 (KGF-2)" in the instant claims can be interpreted to mean several variants, particularly truncated forms of KGF-2. Although Applicants contend that the instant claims are directed to a specific type of KGF-2 variant, Applicants have amended claims 6-8, 10, 16-22, and 25-27 to delete the term "variant of."

The Office Action also asserts a rejection of claims 20-22 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention. The Examiner takes the position that the specification is not enabling for pharmaceutical compositions that could be used for the treatment of any disease. The Examiner also

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takes the position that there is no actual reduction to practice of the claimed invention, or administration of the variant KGF-2 polypeptides for treatment purposes or measurement/detection of expected outcomes of ailments, or recognition of criteria of relief of the symptoms of disease. The Examiner further takes the position that because there is no actual reduction to practice of the claimed invention, Applicants have not provided sufficient evidence that they were in possession of the invention at the time of filing, and therefore, claims 20-22 also fail to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph. Applicants traverse these grounds of rejection.

To satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, the claimed invention must enable one of ordinary skill in the art to make and use the invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Among the factors to be considered in determining whether any necessary experimentation is "undue" are the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d at 737.

Claims 20-22 are directed to pharmaceutical compositions comprising ΔN29 KGF-2 and a pharmaceutically acceptable vehicle. The specification defines a pharmaceutical composition as a composition that includes a therapeutically-effective or prophylatically-effective amount of a KGF-2 protein product in admixture with an acceptable vehicle (p. 43, ln. 22-25). The specification describes several pharmaceutically and physiologically acceptable vehicles that can be combined with the KGF-2 protein of the invention to form a suitable pharmaceutical composition (p.43, ln. 29 to p. 46, ln. 21). The specification further describes procedures for determining acceptable dosages for use in administering the pharmaceutical compositions of the invention (p. 47, ln. 10 to p. 48, ln. 8). In addition, the specification discloses that because the KGF-2 proteins of the invention can be used, *inter alia*, to modulate epithelial cell proliferation in the gastrointestinal tract, the KGF-2 proteins of the invention are useful for treating or preventing diseases and disorders of the gastrointestinal tract (p. 54, ln. 5 to p. 61, ln. 4). The specification further discloses that a pharmaceutical composition comprising ΔN29 KGF-2 and a pharmaceutically acceptable vehicle is

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effective in preventing chemotherapy-induced pulmonary fibrosis in rats (Example 3), an art-recognized animal model for chemotherapy-induced pulmonary disorders (Yi *et al.*, 1996, "Keratinocyte growth factor ameliorates radiation- and bleomycin-induced lung injury and mortality," *Am. J. Pathol.* 149:1963-70). In view of the teachings of the instant specification, Applicants contend that one of ordinary skill in the art could readily make and use the pharmaceutical compositions of the invention without undue experimentation, and therefore, respectfully request that this ground of rejection be withdrawn.

With respect to the Examiner's position that there is no actual reduction to practice of the claimed invention, or administration of the variant KGF-2 polypeptides for treatment purposes or measurement/detection of expected outcomes of ailments, or recognition of criteria of relief of the symptoms of disease, Applicants contend that this ground of rejection would be more properly characterized as a rejection under 35 U.S.C. § 101. *See In re Brana*, 51 F.3d 1560, 1564 (Fed. Cir. 1995)("[I]f a claimed invention does not have utility, the specification cannot enable one to use it."); *see also*, "Example 3: Therapeutic Proteins" *in Revised Interim Utility Guidelines Training Materials* (describing a hypothetical specification disclosing a therapeutic protein having a specified amino acid sequence and further disclosing "alternate administration techniques and dosages that are very specific, conventional techniques for protein administration"). The Examiner's argument appears to be that because the specification does not contain an actual reduction to practice – presumably a showing that the pharmaceutical compositions of the invention can be used to prevent or treat disease *in humans* – the pharmaceutical compositions of the invention lack utility and therefore, the specification cannot enable one of ordinary skill in the art to use the pharmaceutical compositions.

As noted above, however, the specification discloses, *inter alia*, that a pharmaceutical composition comprising ΔN29 KGF-2 and a pharmaceutically acceptable vehicle is effective in preventing chemotherapy-induced pulmonary fibrosis in rats. *In re Brana* reaffirms the principle that "one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans." *In re Brana*, 51 F.3d at 1567 (quoting *In re Krimmel*, 292 F.2d 948, 953 (C.C.P.A. 1961)).

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Moreover, *In re Brana* notes that "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." *Id.* at 1568. Applicants contend that the specification describes an actual reduction to practice of the pharmaceutical compositions of the invention in rats, and that under *In re Brana*, this is sufficient to establish that the pharmaceutical compositions have utility. Applicants also contend that because the pharmaceutical compositions of the invention have utility, it is possible for the specification to enable claims to the pharmaceutical compositions. Finally, Applicants contend that the specification, in fact, enables claims to the pharmaceutical compositions of the invention, as described above. Because one of ordinary skill in the art could readily make and use the pharmaceutical compositions of the invention using the teachings of the specification and information known in the art, Applicants respectfully request that this ground of rejection be withdrawn.

With respect to the Examiner's position that because there is no actual reduction to practice of the claimed invention, Applicants have not provided sufficient evidence that they were in possession of the invention at the time of filing, Applicants first contend that the use of a pharmaceutical composition comprising ΔN29 KGF-2 and a pharmaceutically acceptable vehicle to prevent chemotherapy-induced pulmonary fibrosis in rats constitutes an actual reduction to practice of the claimed pharmaceutical compositions. However, even if the Examiner were to maintain that the experiments described in Example 3 do not constitute an actual reduction to practice of the claimed pharmaceutical compositions, Applicants note that the *Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, P1, "Written Description" Requirement* ("*Guidelines*") do not require that Applicants show an actual reduction to practice in cases such as this one. Rather, the *Guidelines* merely state that:

> [D]escribing an actual reduction to practice is one of a number of ways to show possession of the invention. ... Actual reduction to practice may be crucial in the relatively rare instances where the level of knowledge and level of skill are such that those of skill in the art cannot describe a composition structurally, or specify a process of making a composition by naming components and combining steps, in such a way as to distinguish the composition with particularity from all others.

Guidelines, 66 Fed. Reg. 1099, 1101 (2001).

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Applicants contend that in addition to teaching a pharmaceutical composition for use in preventing chemotherapy-induced pulmonary fibrosis in rats, an art-recognized animal model system (Yi *et al.*, 1996, *Am. J. Pathol.* 149:1963-70), the specification provides a description of the components of the pharmaceutical compositions of the invention, namely a truncated KGF-2 protein (*i.e.*, ΔN29 KGF-2) and a pharmaceutically acceptable vehicle. Although it would be well within the level of knowledge and skill of one of ordinary skill in the art to select a pharmaceutically acceptable vehicle to combine with the truncated KGF-2 protein of the invention to form a suitable pharmaceutical composition, the instant specification also describes several pharmaceutically and physiologically acceptable vehicles that could be used in the pharmaceutical compositions of the invention. The specification also teaches that the truncated KGF-2 protein of the invention retains KGF-2 activity (*see* Example 2, wherein ΔN29 KGF-2 is used to modulate murine keratinocyte proliferation). Because Example 3 of the specification constitutes an actual reduction to practice, Applicants contend that they were in possession of the invention at the time of filing. Moreover, because the specification contains a description of the truncated KGF-2 protein and pharmaceutically acceptable vehicle that comprise the pharmaceutical compositions of the invention, Applicants contend that the specification provides a description of the pharmaceutical compositions that "distinguish[es] the composition with particularity from all others." For these reasons, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, written description requirement, be withdrawn.

Applicants contend that the rejections based on 35 U.S.C. § 112, first paragraph, have been overcome by amendment or traversed by argument, and respectfully request that the Examiner withdraw each of the rejections made on this basis.

3. Rejections of claims 6-8, 10-22, and 25-27 under 35 U.S.C. § 112, second paragraph

The Office Action asserts a rejection of claims 6-8, 10-22, and 25-27 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner takes the position that the recitation of "[Asn^{71}-Ser^{208}]" in claim 25 is confusing because brackets are also used to indicate deleted words or phrases in the amending of claims. Although 37 C.F.R. § 1.121(c)(1)(ii) now

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permits Applicants to use "any equivalent marking system" to indicate changes in amended claims, Applicants have amended claim 25 to delete the term "[Asn^{71}-Ser^{208}]" and recite the truncated KGF-2 protein of the invention so that this recitation complies with 37 C.F.R. §§ 1.821(b) and (d) and 1.822(d). Applicants contend that claim 25, as amended, satisfies the definiteness requirement of 35 U.S.C. § 112, second paragraph, and that this ground of rejection has therefore been overcome by amendment.

The Examiner also takes the position that claim 25 is indefinite because it recites the truncated KGF-2 protein of the invention using three-letter amino acid abbreviations. As suggested by the Examiner, Applicants have amended claim 25 to recite the truncated KGF-2 protein of the invention in the conventional form (MPEP § 2423.03), thereby complying with 37 C.F.R. §§ 1.821(b) and (d) and 1.822(d). Applicants contend that claim 25, as amended, satisfies the definiteness requirement of 35 U.S.C. § 112, second paragraph, and that this ground of rejection has therefore been overcome by amendment.

Applicants contend that the rejections based on 35 U.S.C. § 112, second paragraph, have been overcome by amendment, and respectfully request that the Examiner withdraw each of the rejections made on this basis.

4. Rejections of claims 10-16, 18-19, and 25-27 under 35 U.S.C. § 102

The Office Action asserts a rejection of claims 10-16, 18-19, and 25-27 under 35 U.S.C. § 102(b), as being anticipated by PCT International Pub. No. WO 96/25422 (the '422 application), which was published August 22, 1996. The Examiner takes the position that the '422 application teaches fragments, derivatives, or analogs of the polypeptide of SEQ ID NO: 2, and therefore, anticipates claims 10-16, 18-19, and 25-27. Applicants traverse this rejection.

To support a 35 U.S.C. § 102 rejection, a reference must disclose every aspect of the invention against which it is applied. As a general rule, for prior art to anticipate under § 102, each and every element of the claimed invention must be identically disclosed in a single reference. *Corning Glass Works v. Sumimoto Electric*, 9 U.S.P.Q.2d 1962, 1965 (Fed. Cir. 1989). The exclusion of even a single claimed element, no matter how insubstantial or obvious, from a reference is enough to negate anticipation. *Connell v. Sears, Roebuck & Co.*, 220 U.S.P.Q. 1093, 1098 (Fed.

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Cir. 1983). A generic formula does not anticipate a claimed species covered by the formula unless the claimed species can be "at once envisaged" from the formula. MPEP § 2131.02. One of ordinary skill in the art cannot "at once envisage" a claimed species within a generic formula when that generic formula encompasses a vast number of species. *Id.*

The '422 application does not teach a truncated KGF-2 protein comprising residues 66 through 208 of the amino acid sequence set forth in SEQ ID NO: 2 (of the instant application). The '422 application purports to "provide[] novel mature polypeptides which are KGF-2 as well as biologically active and diagnostically or therapeutically useful fragments, analogs and derivatives thereof" (p. 2, para. 4). The '422 application, however, does not define the meaning of the term "fragment," other than to note that the use of this term "when referring to the polypeptide of Figure 1 . . . means a polypeptide which retains essentially the same biological function or activity as such polypeptide" (p. 8, para. 4). While the '422 application discloses that the mature form of KGF-2 lacks the putative leader sequence of the full-length, or immature, form of the protein (*i.e.*, the first 36 amino acid residues of the immature form) (p. 5, para. 1 and 3), it does not teach *even a single* KGF-2 fragment. Nor does the '422 application disclose important structural domains within KGF-2 that must be preserved in order to retain KGF-2 biological function or activity. Thus, the '422 application discloses a large genus of KGF-2 fragments, encompassing a vast number of KGF-2 fragment species, without disclosing even a single member of that genus. Applicants contend that the disclosure of a generic class of compounds (*i.e.*, KGF-2 fragments) comprising a vast number of species, wherein not a single species is identified, and wherein no teaching is provided for determining which KGF-2 residues must be preserved in order to retain KGF-2 biological activity, does not anticipate the truncated KGF-2 of the present invention. However, even if the Examiner were to contend that the mature form of KGF-2 disclosed in the '422 application constitutes a KGF-2 fragment (a reading that is contradictory to the understanding of those with ordinary skill in the art), Applicants note that the '422 application does not teach the truncated KGF-2 protein of the invention (*i.e.*, ΔN29 KGF-2). Therefore, Applicants contend that because the '422 application does not disclose each and every element of the claimed invention (namely, a truncated KGF-2 protein comprising residues 66 through 208 of the immature form which retains the biological activity of the mature form), the '422 application does not anticipate the truncated KGF-2 of the invention. For

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these reasons, Applicants respectfully request that this rejection be withdrawn.

The Office Action also asserts a rejection of claims 10-16, 18-19, and 25-27 under 35 U.S.C. § 102(b), as being anticipated by PCT International Pub. No. WO 96/11951 (the '951 application), which was published April 25, 1996. The Examiner takes the position that the '951 application teaches a number of KGF analogs, and therefore, anticipates claims 10-16, 18-19, and 25-27. Applicants contend that the '951 application may not serve as the proper basis for the rejection of claims 10-16, 18-22, and 25-27 under 35 U.S.C. § 102(b).

The instant application is directed to a truncated KGF-2 protein comprising residues 66 through 208 of the amino acid sequence set forth in SEQ ID NO: 2 (ΔN29 KGF-2). The specification teaches that KGF-2 is a member of the fibroblast growth factor family of proteins, and that KGF-2 is also known as fibroblast growth factor-10 (FGF-10) (p. 1, ln. 33 to p. 2, ln. 16). The '951 application is directed to biologically active polypeptide analogs of KGF (p. 5, ln. 23-24), and the '951 application teaches the nucleotide and amino acid sequences of KGF (Fig. 1). While the '951 application does not teach that KGF is also known as FGF-7, an examination of the sequence disclosed in Figure 1 indicates that the KGF disclosed in the '951 application is FGF-7 and not FGF-10. A sequence comparison of the full-length KGF-2/FGF-10 and KGF/FGF-7 proteins indicates that KGF-2/FGF-10 shares only 44% sequence identity (and only 62% sequence similarity) with KGF/FGF-7 (Exhibit A; sequence alignments were performed using MacVector 7.1 (Accelrys, Cambridge, UK) at the default settings). Moreover, a search of the OMIM (Online Mendelian Inheritance in Man) database at the NCBI (National Center for Biotechnology Information) website (http://www.ncbi.nlm.nih.gov) indicates that KGF-2/FGF-10 and KGF/FGF-7 are clearly encoded by different genes, the former being located at 5p13-p12 and the latter being located at 15q15-q21.1. Because the '951 application discloses KGF analogs, and *not* KGF-2 analogs, the '951 application fails to disclose each and every element of the instantly claimed invention (*i.e.*, a truncated KGF-2 protein comprising residues 66 through 208 of the amino acid sequence set forth in SEQ ID NO: 2). The semantic similarity between these molecules is thus contradicted by their distinctly different amino acid sequences and genetic loci, indicating that they are separate and distinct genes and that teachings relating to one are not applicable towards the other. For these reasons, Applicants contend that the '951 application does not anticipate claims 10-16, 18-22, and 25-27 under 35 U.S.C. §

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102(b), and respectfully request that this rejection be withdrawn.

The Office Action also asserts a rejection of claims 10-16, 18-22, and 25-27 under 35 U.S.C. § 102(e), as being anticipated by U.S. Patent No. 5,863,767 (the '767 patent), which issued on January 26, 1999, and which claims the benefit of U.S. Patent App. No. 08/086,427, which was filed on June 29, 1993. The Examiner takes the position that the '767 patent teaches $KGF_{des1-23}$, or an analog thereof that is composed of a portion of an amino acid sequence of mature, full-length KGF, a DNA molecule encoding said fragment, an expression vector, a transformed host containing the DNA molecule, and a method of producing $KGF_{des1-23}$ by culturing the transformed host, and therefore, anticipates claims 10-16, 18-20, and 25-27. The Examiner also takes the position that the '767 patent teaches therapeutic compositions containing $KGF_{des1-23}$ in a pharmaceutical carrier, and therefore, anticipates claims 20-22. Applicants contend that the '767 patent may not serve as the proper basis for the rejection of claims 10-16, 18-22, and 25-27 under 35 U.S.C. § 102(e).

As described above, the instant application is directed to a truncated KGF-2 protein comprising residues 66 through 208 of the amino acid sequence set forth in SEQ ID NO: 2 (ΔN29 KGF-2). The specification teaches that KGF-2 is a member of the fibroblast growth factor family of proteins, and that KGF-2 is also known as fibroblast growth factor-10 (FGF-10) (p. 1, ln. 33 to p. 2, ln. 16). The '767 patent is directed to a fragment of KGF, $KGF_{des1-23}$, and analogs thereof (col. 1, ln. 12-13). The '767 patent teaches that KGF is a member of the fibroblast growth factor family of proteins, and that KGF is also known as fibroblast growth factor-7 (FGF-7) (col. 1, ln. 21-23). As described above, differences in sequence and chromosomal location indicate that KGF-2/FGF-10 and KGF/FGF-7 are encoded by different genes. Moreover, a sequence comparison of the truncated KGF-2 protein of the invention and the truncated KGF protein disclosed in the '767 patent indicates that these proteins share only 52% sequence identity (and only 69% sequence similarity) (Exhibit B). Because the '767 patent discloses KGF analogs, and *not* KGF-2 analogs, the '767 patent fails to disclose each and every element of the instantly claimed invention (*i.e.*, a truncated KGF-2 protein comprising residues 66 through 208 of the amino acid sequence set forth in SEQ ID NO: 2) and cannot anticipate the rejected claims. For this reason, Applicants contend that the '767 patent does not anticipate claims 10-16, 18-22, and 25-27 under 35 U.S.C. § 102(e), and respectfully request that this rejection be withdrawn.

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Applicants contend that the rejections based on 35 U.S.C. § 102 have been traversed by argument, and respectfully request that the Examiner withdraw each of the rejections made on this basis.

5. Rejections of claims 10-16, 18-19, and 25-27 under 35 U.S.C. § 103(a)

The Office Action asserts a rejection of claims 10-16, 18-19, and 25-27 under 35 U.S.C. § 103(a), as being unpatentable over PCT International Pub. No. WO 97/20929 (the '929 application), which was published June 12, 1997, in view of U.S. Patent No. 5,863,767 (the '767 patent), which issued on January 26, 1999, and which claims the benefit of U.S. Patent App. No. 08/086,427, which was filed on June 29, 1993. The Examiner takes the position that the '929 application teaches recombinant KGF-2/FGF-10, related DNA, vectors containing the DNA, and host cells containing the vectors, but acknowledges that because the '929 application is in Japanese, it is unclear whether the document teaches N-terminal truncations of KGF-2. The Examiner also takes the position that the '767 patent teaches truncated forms of KGF-2 possessing biological activity (as indicated, according to the Examiner, by the title of the '767 patent itself). The Examiner contends that it would have been obvious to one of ordinary skill in the art to have combined the teachings of the '929 application and those of the '767 patent to obtain N-terminally truncated forms of KGF-2 possessing enhanced biological activity. Applicants traverse this rejection.

An analysis of obviousness must be based on the following factual inquiries: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art at the time the invention was made; and (4) objective evidence of nonobviosuness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Moreover, where claimed subject matter has been rejected as obvious in view of a combination of prior art reference, a proper analysis under § 103 also requires consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). A rejection under 35 U.S.C. § 103 must be supported using subject matter that was in the prior art under 35 U.S.C. § 102.

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Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1568 (Fed. Cir. 1987).

Applicants contend that the scope and content of the prior art cited by the Examiner as the basis for this rejection cannot be readily determined because the '929 application is in Japanese and an English-language translation of this reference has not been provided (the Examiner has acknowledged that in preparing the instant Office Action, an English-language translation of this reference was not considered). The English-language translation of the '929 application abstract (obtained at http://ipdl.wipo.int) suggests that the '929 application is directed to recombinant *full-length* KGF-2 proteins, rather than to truncated forms of KGF-2. Moreover, Applicants note that Applicants' instant application was filed under 35 U.S.C. § 371 from International Application No. PCT/ US97/18607, which was filed on October 15, 1997, claiming the benefit of U.S. Provisional Patent App. Nos. 60/033,046 (filed December 11, 1996); 60/032,781 (filed December 6, 1996) and 60/028,493 (filed October 15, 1996). Therefore, even if the Examiner has accurately determined the scope and content of the '929 application, Applicants contend that since the '929 application was published on June 12, 1997, the subject matter of this reference is not in the prior art to the instant application under 35 U.S.C. § 102 as applied to the claims under 35 U.S.C. § 103.

Having established that the '929 application is not properly applied to the pending claims because it is not prior art, Applicants contend that the asserted ground of rejection under 35 U.S.C. § 103 is traversed. However, in an effort to address all issues presented in the Office Action, Applicants also contend that the '767 patent discloses KGF/FGF-7 analogs, *rather than* KGF-2/FGF-10 analogs as the instant Office Action asserts. As discussed in paragraph 4, the '767 patent is directed to a fragment of KGF, $KGF_{des1\text{-}23}$, and analogs thereof. The '767 patent teaches that KGF is a member of the fibroblast growth factor family of proteins, and that KGF is also known as fibroblast growth factor-7 (FGF-7). A sequence comparison of the truncated KGF-2 protein of the invention and the truncated KGF protein disclosed in the '767 patent indicates that these proteins share only 52% sequence identity (and only 69% sequence similarity) (Exhibit B).

In contrast, the claims of the instant application are directed to a truncated KGF-2 protein comprising residues 66 through 208 of the amino acid sequence set forth in SEQ ID NO: 2 (ΔN29 KGF-2), and *not* a truncated KGF protein. Applicants contend that the '767 patent does *not* teach one of ordinary skill in the art how to make truncated forms of KGF-2. Applicants also contend that

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it would *not* have been obvious to one of ordinary skill in the art where to truncate KGF-2, *without* destroying KGF-2 activity, using the teachings of the '767 patent. In the absence of the teachings of the instant application, one of ordinary skill in the art would not have known that a KGF-2 protein comprising residues 66 through 208 of the amino acid sequence set forth in SEQ ID NO: 2 would retain KGF-2 activity. Applicants further contend that neither the '929 application nor the '767 patent provide a suggestion or motivation to truncate KGF-2. For these reasons, Applicants contend that the '929 application and the '767 patent do not render claims 10-16, 18-22, and 25-27 obvious under 35 U.S.C. § 103(a), and respectfully request that this rejection be withdrawn.

The Office Action also asserts a rejection of claims 6-8 under 35 U.S.C. § 103(a), as being unpatentable over the '929 application, in view of the '767 patent, as applied to claims 10-16, 18-19, and 25-27, and further in view of McGwire *et al.*, 1996, *J. Biol. Chem.* 271(14): 7903-09. The Examiner takes the position that the '929 application teaches recombinant KGF-2/FGF-10, related DNA, vectors containing the DNA, and host cells containing the vectors, but acknowledges that because the '929 application is in Japanese, it is unclear whether the document teaches N-terminal truncations of KGF-2. The Examiner also takes the position that the '767 patent teaches truncated forms of KGF-2 possessing biological activity (as indicated, according to the Examiner, by the title of the '767 patent itself), but acknowledges that the '767 patent does not teach other modifications of truncated KGF-2 that can enhance its stability. The Examiner further takes the position that McGwire *et al.* teach the effects of N-glycosylation and N-terminal cleavage on intracellular stability. The Examiner contends that it would have been *prima facie* obvious to one of ordinary skill in the art to combine the teachings of the '929 application and those of the '767 patent to generate truncated forms of KGF-2, and to further combine these teachings with McGwire *et al.* to N-glycosylate the truncated forms of KGF-2 to enhance their stability even further. With respect to claim 8, the Examiner further contends that additional stability-enhancing modifications, such as conjugation with a water-soluble polymer, also would have been obvious to one of ordinary skill in the art. Finally, the Examiner contends that the motivation to make such combinations is provided by the need to have stable forms of KGF-2 having enhanced biological activity for *in vitro* and *in vivo* use. Applicants traverse this rejection.

Applicants addressed the unavailability of the '929 application as prior art and the scope and

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content of both the '929 application and the '767 patent in analyzing the instant Office Action's first rejection under 35 U.S.C. § 103. As for the scope and content of McGwire *et al.*, this reference teaches that site-specific mutagenesis of catalytic, zinc-binding, N-glycosylation, and glycosyl phosphatidylinositol addition sites of Leishmanolysin (gp63; a HEXXH metalloprotease expressed in the parasitic protozoan Leishmania) affects N-terminal end cleavage, intracellular stability, and extracellular exit. McGwire *et al.* does *not*, however, teach the site-specific mutagenesis of *any* proteins *other than* gp63, or how to modulate the glycosylation of proteins other than gp63, or whether intracellular stability would be affected by modulating glycosylation of proteins other than gp63.

As discussed above, the claims of the instant application are directed to a truncated KGF-2 protein (ΔN29 KGF-2). Applicants addressed the reasons why the '929 application and the '767 patent do not render claims 10-16, 18-22, and 25-27 obvious under 35 U.S.C. § 103(a) in analyzing the instant Office Action's first rejection under 35 U.S.C. § 103. With respect to the second ground of rejection, Applicants contend that even if the combination of the '929 application and the '767 patent rendered truncated forms of KGF-2 obvious – which Applicants contend it cannot and does not – McGwire *et al.* does *not* teach one of ordinary skill in the art how to make glycosylated forms of KGF-2 or whether the modulation of KGF-2 glycosylation would affect intracellular stability. Applicants also contend that McGwire *et al.* does not provide a suggestion or motivation to one of ordinary skill in the art to glycosylate KGF-2 or any protein other than gp63. Applicants further contend that neither the '929 application nor the '767 patent provides such a suggestion or motivation for so modifying KGF-2. For these reasons, Applicants contend that the Examiner's combination of the '929 application, in view of the '767 patent, and further in view of McGwire *et al.*, does not render claims 6-8 obvious under 35 U.S.C. § 103(a), and Applicants respectfully request that this rejection be withdrawn.

CONCLUSIONS

Applicants respectfully contend that all conditions of patentability are met in the pending claims as amended. Allowance of the claims is thereby respectfully solicited.

If the Examiner believes it to be helpful, he or she is invited to contact the undersigned

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representative by telephone at (312) 913-0001.

Respectfully submitted,
McDonnell Boehnen Hulbert & Berghoff

Dated: May 6, 2002

By: _____
Donald L. Zuhn, Ph.D
Reg. No. 48,710

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EXHIBIT A

```
KGF-1 (FGF-7) vs. KGF-2 (FGF-10)

   Aligned Length = 209   Gaps = 4
   Identities = 92 (44%)   Similarities = 38 (18%)

KGF-1 (FGF-7)     1 MHKWILTWILPTLLYRS-----CFHIICLVGTISLACNDMTPEQMATNVN  45
KGF-2 (FGF-10)    1 MWKWILTHCASAFPHLPGCCCCCFLLLFLVSSVPVTCQALGQDMVSPEAT  50
                    * *****     .              ** .. ** .. ..*. .  .  .  .

KGF-1 (FGF-7)    46 CSS------PE---RHTRSYDYMEGGDIRVRRLFCRTQWYLRIDKRGKVK  86
KGF-2 (FGF-10)   51 NSSSSSSFSSPSSAGRHVRSYNHLQG-DVRWRKLFSFTKYFLKIEKNGKVS  99
                      **       *    ** ***  ..* *.* *.**. *. .*.*.* ***

KGF-1 (FGF-7)    87 GTQEMKNNYNIMEIRTVAVGIVAIKGVESEFYLAMNKEGKLYAKKECNED 136
KGF-2 (FGF-10) 100 GTKKENCPYSILEITSVEIGVVAVKAINSNYYLAMNKKGKLYGSKEFNND 149
                    **.     * *.** .* .*.**.* . * .****** ****  ** * *

KGF-1 (FGF-7)    137 CNFKELILENHYNTYASAKWTHNGGEMFVALNQKGIPVRGKKTKKEQKTA 186
KGF-2 (FGF-10)   150 CKLKERIEENGYNTYASFNWQHNGRQMYVALNGKGAPRRGQKTRRKNTSA 199
                      *  ** * ** ******  * *** .*.**** ** * **.**.. . .*

KGF-1 (FGF-7)    187 HFLPMAIT  194
KGF-2 (FGF-10)   200 HFLPMVVHS 208
                      ***** .


ClustalW (v1.4) multiple sequence alignment

2 Sequences Aligned              Alignment Score = 659
Gaps Inserted = 4                Conserved Identities = 92

Pairwise Alignment Mode: Slow
Pairwise Alignment Parameters:
    Open Gap Penalty = 10.0   Extend Gap Penalty = 0.1
    Similarity Matrix: blosum

Multiple Alignment Parameters:
    Open Gap Penalty = 10.0   Extend Gap Penalty = 0.0
    Delay Divergent = 40%     Gap Distance = 8
    Similarity Matrix: blosum
```

EXHIBIT B

KGF truncation vs. KGF-2 truncation

```
   Aligned Length = 144   Gaps = 1
   Identities = 75 (52%)   Similarities = 25 (17%)

KGF truncation     1    SYDYMEGGDIRVRRLFCRTQWYLRIDKRGKVKGTQEMKNNYNIMEIR  47
KGF-2 truncatio    1 HVRSYNHLQG-DVRWRKLFSFTKYFLKIEKNGKVSGTKKENCPYSILEIT  49
                       **  ..* *.* *.**. *. .*.*.* *** **.      * *.**

KGF truncation    48 TVAVGIVAIKGVESEFYLAMNKEGKLYAKKECNEDCNFKELILENHYNTY  97
KGF-2 truncatio   50 SVEIGVVAVKAINSNYYLAMNKKGKLYGSKEFNNDCKLKERIEENGYNTY  99
                      .* .*.**.* . * .****** ****  ** * **  ** * ** ****

KGF truncation    98 ASAKWTHNGGEMFVALNQKGIPVRGKKTKKEQKTAHFLPMAIT  140
KGF-2 truncatio  100 ASFNWQHNGRQMYVALNGKGAPRRGQKTRRKNTSAHFLPMVVHS 143
                      **  * *** .*.**** ** * **.**.. . .****** .
```

```
ClustalW (v1.4) multiple sequence alignment

2 Sequences Aligned              Alignment Score = 526
Gaps Inserted = 1                Conserved Identities = 75

Pairwise Alignment Mode: Slow
Pairwise Alignment Parameters:
    Open Gap Penalty = 10.0   Extend Gap Penalty = 0.1
    Similarity Matrix: blosum

Multiple Alignment Parameters:
    Open Gap Penalty = 10.0   Extend Gap Penalty = 0.0
    Delay Divergent = 40%     Gap Distance = 8
    Similarity Matrix: blosum
```

AMENDMENTS TO THE CLAIMS

Marked Up Versions of Amended Claims under 37 C.F.R. 1.121(c)(1)(ii)

6. (Twice Amended) The ~~variant of~~ KGF-2 protein according to Claim 25, wherein said amino acid sequence is nonglycosylated.

7. (Twice Amended) The ~~variant of~~ KGF-2 protein according to Claim 25, wherein said amino acid sequence is glycosylated.

8. (Twice Amended) A chemical derivative comprising a water-soluble polymer conjugated to ~~a variant of~~ the KGF-2 protein according to Claim 25.

10. (Twice Amended) A polynucleotide encoding the ~~variant of~~ KGF-2 protein according to Claim 25.

16. (Twice Amended) A method comprising the step of isolating a ~~variant of~~ keratinocyte growth factor-2 (KGF-2) protein from a host cell containing a polynucleotide of Claim 10 cultured under conditions allowing the expression of the ~~variant of~~ KGF-2 protein by said host cell.

17. (Amended) The method according to Claim 16 comprising the step of modifying the isolated ~~variant of~~ KGF-2 protein to generate a compound capable of stimulating the production of epithelial cells.

18. (Twice Amended) A method comprising the steps of:

(a) culturing a prokaryotic or eukaryotic host cell containing a polynucleotide of Claim 10; and

(b) maintaining said host cell under conditions allowing the expression of a ~~variant of~~ keratinocyte growth factor-2 (KGF-2) protein by said host cell.

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19. (Twice Amended) The ~~variant of~~ KGF-2 protein according to Claim 25 which is the recombinant expression product of a prokaryotic or eukaryotic host cell containing an exogenous polynucleotide of Claim 10.

20. (Twice Amended) A pharmaceutical composition comprising the ~~variant of~~ KGF-2 protein according to Claim 25 in association with a pharmaceutically acceptable vehicle.

21. (Twice Amended) A pharmaceutical composition comprising a ~~variant of~~ keratinocyte growth factor-2 (KGF-2) protein isolated in accordance with the method of Claim 26 in association with a pharmaceutically acceptable vehicle.

22. (Twice Amended) A pharmaceutical composition comprising a ~~variant of~~ keratinocyte growth factor-2 (KGF-2) protein isolated in accordance with the method of Claim 27 in association with a pharmaceutically acceptable vehicle.

25. (Twice Amended) A ~~variant of~~ keratinocyte growth factor-2 (KGF-2) protein selected from the group of consisting of:

(a) a KGF-2 protein consisting of residues 66 through 208 of the amino acid sequences ~~consisting of methionylated or non-methionylated NH_2-His-Val-Arg-Ser-Tyr-[Asn^{71}-Ser^{208}]-COOH~~ set forth in SEQ ID NO: 2; and

(b) a KGF-2 protein consisting of residues 66 through 208 of the amino sequence set forth in SEQ ID NO: 2 and an N-terminal methionine.

26. (Amended) The method of Claims 13, 14 or 15 further comprising isolating a ~~variant of~~ keratinocyte growth factor-2 (KGF-2) protein from said cultured cells or said nutrient medium.

27. (Amended) The method of Claim 18, further comprising after step (b) the following step (c):

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(c) isolating the ~~variant of~~ KGF-2 protein expressed by said host cell.

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PENDING CLAIMS

Clean Versions of Pending Claims under 37 C.F.R. 1.121(c)(3)

6. The KGF-2 protein according to Claim 25, wherein said amino acid sequence is nonglycosylated.

7. The KGF-2 protein according to Claim 25, wherein said amino acid sequence is glycosylated.

8. A chemical derivative comprising a water-soluble polymer conjugated to the KGF-2 protein according to Claim 25.

10. A polynucleotide encoding the KGF-2 protein according to Claim 25.

11. A vector comprising a polynucleotide of Claim 10 operatively linked to an expression control sequence

12. A prokaryotic or eukaryotic host cell containing a polynucleotide of Claim 10.

13. A method comprising culturing the host cell of Claim 12 in a suitable nutrient medium.

14. The method according to Claim 13, wherein said host cell is an *E. coli* cell.

15. The method according to Claim 13, wherein said host cell is selected from a baculovirus cell, COS cell or Chinese hamster ovary cell.

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16. A method comprising the step of isolating a keratinocyte growth factor-2 (KGF-2) protein from a host cell containing a polynucleotide of Claim 10 cultured under conditions allowing the expression of the KGF-2 protein by said host cell.

17. The method according to Claim 16 comprising the step of modifying the isolated KGF-2 protein to generate a compound capable of stimulating the production of epithelial cells.

18. A method comprising the steps of:

(a) culturing a prokaryotic or eukaryotic host cell containing a polynucleotide of Claim 10; and

(b) maintaining said host cell under conditions allowing the expression of a keratinocyte growth factor-2 (KGF-2) protein by said host cell.

19. The KGF-2 protein according to Claim 25 which is the recombinant expression product of a prokaryotic or eukaryotic host cell containing an exogenous polynucleotide of Claim 10.

20. A pharmaceutical composition comprising the KGF-2 protein according to Claim 25 in association with a pharmaceutically acceptable vehicle.

21. A pharmaceutical composition comprising a keratinocyte growth factor-2 (KGF-2) protein isolated in accordance with the method of Claim 26 in association with a pharmaceutically acceptable vehicle.

22. A pharmaceutical composition comprising a keratinocyte growth factor-2 (KGF-2) protein isolated in accordance with the method of Claim 27 in association with a pharmaceutically acceptable vehicle.

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25. (Twice Amended) A keratinocyte growth factor-2 (KGF-2) protein selected from the group of consisting of:

(a) a KGF-2 protein consisting of residues 66 through 208 of the amino acid sequence set forth in SEQ ID NO: 2; and

(b) a KGF-2 protein consisting of residues 66 through 208 of the amino sequence set forth in SEQ ID NO: 2 and an N-terminal methionine.

26. The method of Claims 13, 14 or 15 further comprising isolating a keratinocyte growth factor-2 (KGF-2) protein from said cultured cells or said nutrient medium.

27. The method of Claim 18, further comprising after step (b) the following step (c):

(c) isolating the KGF-2 protein expressed by said host cell.

28. The KGF-2 protein according to Claim 25, wherein at least one domain of the constant region of the heavy chain of human immunoglobulin is fused to the C-terminal end of the KGF-2 protein.

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